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CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

REMARKS

I. Election With Traverse of the Restriction Requirement

Applicants provisionally elect with traverse, GROUP 7 encompassing a point mutation at position 1541,

and elect species wherein 1541 C → T; 1633A; 1666C; the species described in claim 3.

II. Comments In Support Of Traversing The Restriction Requirement

Response to Examiner's Remarks

1. Examiner asserts that Applicants' amendments and remarks necessitated a new restriction. Clarification is requested. The previous response simply amended claim 1 to overcome the applied reference to Turki et al. This reference was the sole basis supporting the alleged lack of unity of invention because the claims did not distinguish over the art.

It is not clear from this amendment why the Examiner deemed it ***necessary*** to issue a new restriction requirement. No reasoning is presented. Neither is it clear how the remarks filed with the amendment necessitated the additional requirement as Examiner provided no explanation.

Clarification of this reasoning is respectfully requested.

2. On the top of page of the action, Examiner applies 37 C.F.R. 1.475(d). However, it is noted that 37 CFR § 1.147 5(d) does not apply. Specifically, this rule does not apply to multiple related products, but to multiple *unrelated* products; e.g., claim 1 to a protein, and claim 2 an antibody to the protein, claim 3 an antisense RNA for inhibiting the expression of the protein. Alternatively, if these three products were together in a Markush group, then 1.475(d) would apply. See 1.1475(e).

In other words, before 1.475(d) can be applied to a Markush claim, the claim must first fail the PCT's unity of invention test, This test is reproduced in the next section.

Support for this interpretation can be found on materials downloaded from the PTO website in the form of a presentation entitled *Unity of Invention Biotechnology Practice* by Special Program Examiner Julie Burke. A few of the more relevant pages are attached herewith.

- The presentation's title page.
- Page 2 indicates that variants of a single gene are not viewed as distinct inventions.
- Page 3 indicates a generic type of Markush claim for sequences.
- Page 4 page gives an example of a proper PCT unity of invention analysis of the a hypothetical group of DNAs used for detecting *Salmonella*.
- Pages 5 and 6 pages indicate the proper application of 37 CFR § 1.1475(d). Specifically, that multiple products must be unrelated in structure and function.

3. Examiner also indicates that "there is no method of making the polynucleotide." Respectfully, § 112 issues do not figure in PCT unity of invention determinations. In case the undersigned has misinterpreted the statement, it is pointed out that the specification discloses the sequence of each PCR and sequencing primers necessary to determine the presence of any of the claimed mutations in a subject's genome.

4. Examiner states "as Applicant points out, each allele is a non-obvious variant of the others." The undersigned respectfully requests that Examiner identify with specificity where within the previous response this concession was made.

It is further pointed out that patentable distinctness between alternatives of a Markush group is irrelevant in the PCT unity of invention inquiry, unless the entire claim (i.e., all alternatives) is not distinguished over the prior art. The prior amendment distinguished the claims over Turki. Issues of obviousness should not arise until examination on the merits ensues.

In sum, Examiner's restriction requirement does not properly follow from the PCT rules regarding Markush practice. See MPEP § Appendix AI Administrative Instructions Under the PCT; part B - Unity of Invention.

Application of the PCT Unity of Invention Rules Demonstrates That the Present Restriction Requirement Should be Withdrawn in its Entirety

The rule reads as follows:

f) **"Markush Practice."** The situation involving the so-called "Markush practice" wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2. **In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.**

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) **all alternatives have a common property or activity,** and

(B)(1) **a common structure is present, i.e., a significant structural element is shared by all of the alternatives,** or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

(ii) In paragraph (f)(i)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together.

(iii) In paragraph (f)(i)(B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

(iv) The fact that the alternatives of a Markush grouping can be differently classified shall not, taken alone, be considered to be justification for a finding of a lack of unity of invention.

(v) When dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner. Reconsideration does not necessarily imply that an objection of lack of unity shall be raised.

(Emphases added).

Unity of invention exists between the alternatives of a Markush group, when the alternatives possess a technical interrelationship and share a corresponding special technical feature. This arises when a claim satisfies (f)(i)(A) and either of (f)(i)(B)(1) or (f)(i)(B)(2).

The following analysis is based on these rules for PCT unity of invention compliance of the instantly claimed Markush group of claim 1.

Claim 1 recites a Markush group of 12 point mutations in the human beta-2 adrenergic gene. This gene is depicted in Figure 1 as being 2679 base pairs in length. Further, the role of these mutants as diagnostic tools for examining potential malfunctions of the autonomic nervous system (ANS) are described from page 4-6.

The stepwise analysis is directed toward determining whether the Markush group in claim 1 satisfies (f)(i)(A) and either of (f)(i)(B)(1) or (f)(i)(B)(2).

(f)(i)(A) all alternatives have a common property or activity, and ...

Applicants describe the mutants as being indicative of the state of of ANS functioning. Some of the relevant functions of the ANS are described in the specification; e.g., blood pressure, heart rate, noradrenalin levels, etc. See specification, page 6. All of the claimed variants relate to ANS functioning.

Applicants respectfully suggest that the claims satisfy criterion A) of the PCT test.

Examiner has, without any evidence or solid scientific reasoning, stated that the mutants are "directed to an indecipherable number of diseases." This is factually

incorrect and purely speculative; and as such it is not sufficient as a basis of maintaining the restriction requirement.

Further, Examiner's conclusion runs counter to the longstanding rule of *In re Marzocchi* (169 USPQ 367, 370 (CCPA 1971)), see MPEP § 2163 (*"A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption."*) Applicants have clearly described the aspects of ANS functioning that relate to the gene and its variants. *Marzocchi* states that only scientific evidence or solid scientific reasoning can rebut statements in Applicants' disclosure.

No such evidence or reasoning is offered to support the conclusion that the claimed variants relate to an indecipherable number of diseases.

The alternative mutants in claim 1 clearly have the same technical interrelationship. It is submitted that criterion A) is satisfied.

(f)(i)(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives...

Each of the twelve point mutations represent a single base change in a sequence of 2679 base pairs. Therefore, each of the mutants possesses 2677 bp out of 2679 bp. Each individual mutant shares 99.99% structural identity.

Similarly, a variant possessing all of these mutations would share [2679-12=] 2667 out of 2679 base pairs. Therefore a mutant harboring all of the base substitutions of claim 1 would share no less than 99.5% of the same structure as any other single point mutant, or any combination of multiple-replacement mutants.

In view of the fact that *any* single or multiple-replacement mutant cannot differ by more than 99.5%, it is clear that these mutants share a common structure as required by the PCT guidelines.

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III. CONCLUSION

The foregoing discussion clearly indicates that the examination instructions provided in the Administrative Instruction Under the PCT, Annex B, Part 1, paragraphs (f)(i)(A) and (f)(i)(B)(1) are both satisfied. In accordance with PCT Rule 13.2, the variants described in claim 1 are of a similar nature and therefore possess unity of invention.

In accordance, Applicants earnestly solicit withdrawal of the restriction requirement.

Applicants believe in good faith that they have traversed to two restriction requirements issued 14 months apart. It is respectfully requested that early consideration and notification of the status of the instant restriction requirement be communicated to the undersigned.

Respectfully Submitted,

Norris, McLaughlin & Marcus
220 East 42nd Street
New York, NY 10017
Telephone (212) 808-0700
Facsimile (212) 808-0844

Theodore Gottlieb, PhD
Reg. Nr. 42,597